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Visual Effects Accompanying TEPP-Induced Miosis

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TOXICOLOGY PROGRAM
Technology Branch
Communicable Disease Center
Atlanta 22, Ga.

WILLIAM M. UPHOLT, Ph.D.
GRIFFITH E. QUINBY, M.D., M.P.H.
GORDON S. BATCHELOR, M.S.
Wenatchee, Wash.
and
JAMES P. THOMPSON, M.D.
Yakima, Wash.

Pilots and others have long recognized the miosis which is frequently a consequence of spraying tetraethylpyrophosphate (TEPP) dust by aircraft. This effect of TEPP often occurs without symptoms referable to any part of the body except the eyes. Parathion (O,O-diethyl O-para-nitrophenyl thiophosphate) may also produce miosis, but it does so less frequently, and when it does the eye signs and symptoms are usually accompanied by general, systemic illness. The reason for the difference in clinical effect is not entirely clear but probably involves, among other things, the difference in molecular weight and vapor pressure of the two compounds.

Various flying accidents have been blamed on the effects of organic phosphates on pilots.* Two complaints which are occasionally made by the pilots themselves involve an inability to judge distance and a sensation that things are darker than the time of day, the season, and the weather justify.

A study in 1953 of the visual fields of 15 pilots and 2 other persons before, during, and after occupational exposure to TEPP did not reveal any meaningful change. However, only one pilot in this series was available for study of visual fields at a time when he actually had miosis. A much greater diversity of tests conducted during miosis seemed to be required to explain the reported disturbances of function.

The dosage level in the eye required to contract the pupil to 1 mm. diameter was worked out in an intensive study of one volunteer at three dosage levels. The study served to establish techniques for conducting a battery of ophthalmological tests. Instillation of 1 drop (about 0.01 cc.) of 0.0125% TEPP and later of 1 drop of 0.05% TEPP produced no measurable effect. Instillation of 2 drops (about 0.02 cc.) of 0.05% TEPP produced slight miosis and a slight increase of near accommodation. Maximal miosis was produced by 2 drops of 0.1% TEPP, the pupils being fixed at 1 mm. diameter. A fourth drop did not cause further miosis or other observed change. Visual acuity (Snellen), peripheral fields (Ferree-Rand simplified

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From the Communicable Disease Center, Public Health Service, U. S. Department of Health, Education and Welfare, Atlanta, Ga. Senior Scientist (Dr. Upholt); Senior Surgeon (Dr. Quinby); Entomologist (Mr. Batchelor), and Consultant in Ophthalmology (Dr. Thompson).

*References 1 and 4.

perimeter), depth perception (Howard-Dolman), color vision (Ishihara), and subjective perception all remained within normal limits. The near point as measured by the Prince Rule moved from a predosage distance of about 13 cm. to 3.8 cm. for the right eye and 4.5 cm. for the left eye.

The next logical course of investigation was to induce miosis in a number of pilot-volunteers. Six men with no previous exposure during the spray season in which the tests were made were selected from a group of commercial dusting pilots and their occupational associates by screening with a medical and ophthalmologic history followed by medical examinations.

The TEPP used in this experiment consisted of 40% tetraethylpyrophosphate and 60% related organic phosphates. Each drop (0.01 ml.) of 0.1% technical (40%) TEPP contained 0.009 mg. of technical TEPP in peanut oil. The maximum dose (2 drops of 0.1% into each eye) totaled 0.036 mg. For the average body weight of 83 kg., the maximum dosage rate was 0.0004 mg/kg.

For each dosage level, the volunteers were given batteries of tests at intervals of one hour. About one week elapsed between the different TEPP dosages. With the minor exceptions noted, each battery of tests consisted of the following 23 tests.

The first group of tests in each battery was performed with the Ortho-Rater † for far vision—(1) vertical phoria; (2) lateral phoria; (3, 4, 5) acuity, eyes together and separately; (6) binocular depth perception; (7) color vision—and for near vision—(8, 9, 10) acuity, eyes together and separately; (11) vertical phoria; (12) lateral phoria. A transilluminated Snellen chart and associated rheostat ‡ were used to make the following tests: (13) Bilateral acuity. (This was checked at the 20/20 level on all candidates with full power load in the chart-lamp circuit. Tests of more critical acuity were not in order because subsequent threshold tests required the use of the 20/20 test line, which was the only one homogeneously illuminated at various intensities.) (14) Threshold of light intensity required for reading. (Following the test of bilateral acuity, the light intensity was turned down by means of the rheostat until the volunteer could not distinguish the letters and then turned up until he could. The reading in arbitrary units, 135 for the entire scale, was recorded.) (15) Threshold of light intensity required for perception. (For the tests at the highest dosage level, 2 drops of 0.1% TEPP, the rheostat reading was also recorded at the first point at which the subject could distinguish the faint pinkish light in the chart, i.e., the threshold of minimum light perception. As the power delivered by the rheostat to the light circuit was reduced, the quality of the light changed from incandescent white to orange and then to a faint pinkish glow before disappearing entirely.) The Prince Rule and No. 3 Jaeger print card were used to test (16) accommodation for near vision. The Snellen chart and appropriate lenses held in the usual test frame were used to test (17) accommodation for far vision in respect to positive lenses; (18) accommodation for far vision in respect to negative lenses. A camera was used to record (19, 20) pupil size and reaction to light. (The eye was photographed in a darkroom with normal lighting. After adaptation in the dark for five minutes, the eye was again photographed.) The Hare perimeter was used to determine (21) field of vision. (Readings were taken for white on the vertical and horizontal axes of the perimeter.) The Schiøtz tonometer was used to measure (22) ocular tension. Blood was drawn from the ear to determine

† Bausch and Lomb Optical Company, Professional Model.
‡ Fisher Scientific Powerstat, Type 116, output range 135 volts.

(23) plasma and red blood cell cholinesterase levels, by use of a modification of the Michel electrometric procedure.[8] (Blood was drawn on two occasions before any TEPP was instilled into the eyes and again at the end of the last battery of tests at each dosage level.)

The results of the study are summarized in Table 1. Where there were

TABLE 1.—*Selected Ophthalmologic Measurements of Certain Functions of the Eyes of Pilots into Which TEPP Had Been Instilled**

Function	Condition of Test	Unit of Measure	Eye†	Dosage Level and Time After Dosage					
				1 Drop Peanut Oil (Control)		2 Drops 0.1% TEPP			
				Before Dose	After 1 Hr.	Before Dose	1 Hr.	2 Hr.	3 Hr.
Diameter of pupil	Illuminated	Mm.	L	5.4	4.6	4.5	1.9	1.9	1.8
	Dark	Mm.	L	6.7	6.6	5.3	1.9	1.9	2.0
Acuity	Minimum light to read Snellen 20/20	Rheostat units	B	33.3	38.2	29.7	35.5	32.7	33.0
Light perception	Minimum light (pink)	Rheostat units	B			19.9	17.5	17.2	16.4
Accommodation	Prince Rule	Cm.	L	13.3	13.3	12.3	6.1	6.8	7.9
	Snellen chart	Pos. diopters	R	1.58	1.92	1.92	2.35	2.46	2.42
		Neg. diopters	R	2.53	3.17	2.71	5.96	6.16	7.60
Acuity	Ortho-Rater, far vision	Ortho-Rater scored units	R	10.5	11.8	11.8	9.5	10.2	10.0
			B	11.3	12.3	11.5	9.3	9.7	9.5
			L	11.3	11.5	12.7	9.5	10.3	10.7
	Ortho-Rater, near vision	Same	R	11.5	11.5	11.8	10.5	10.3	10.0
			B	12.2	11.0	12.5	10.0	10.0	9.7
			L	11.3	12.0	11.8	9.7	10.3	10.3
Depth perception	Ortho-Rater	Ortho-Rater units	B	6.7	5.3	6.5	6.3	5.8	6.3
Visual fields	Hare perimeter, horizontal	Degrees subtended	L	135.7	138.9	133.9	127.8	133.9	138.2
	Hare perimeter, vertical	Same	L	109.0	111.7	108.3	109.3	109.6	99.3
Ocular tension	Schiötz tonometer	Mm. of Hg	R		19.3				16.5
			L		17.7				14.3

* Mean values from six subjects.
† Left eye, right eye, or both eyes, as indicated.

no notable differences in the two eyes, only data for the left eye have been given in the Table. Some tests which gave negative or normal results at all dosage levels have been omitted from the Table.

The production of maximal miosis, at least to the point of fixing the pupils, was considered one of the requisites of this study. Fixation of the pupils with concomitant effects was obtained consistently only with 2 drops of 0.1% TEPP spaced 30 minutes apart and not with a single drop.

Subjectively the maximum dosage caused mild headaches, sensations of pressure in the eyeballs or over the frons, slight burning of the lids, "running" or "stopped-up" nose, and a sensation that "things were getting darker." These symptoms passed their peak during the first or second hour. Four of the pilots stated, upon self-inspection in the mirror, that their pupils were not as small following the experimental exposures as they were following occupational exposure in the summer. One pilot believed that the experimental miosis was as severe as he had ever experienced in applying TEPP by airplane. The sixth man had had insufficient prior exposure to make a significant comparison.

At the highest dosage level, the subjective complaints of reduction of light perception were corroborated by the Snellen chart light-threshold test

and also by the minimum perception of light in the same back-illuminated chart.

The Prince Rule test showed greatest accommodation for near vision at the one-hour observation battery (30 minutes after the second drop). The lens test for far accommodation revealed a gradually increasing accommodation, particularly to negative lenses, at least until the third hour. One of the subjects was tested at the fifth hour also and was found to have undergone no further change in this respect. The changes in accommodation may be accounted for, at least in part, on a physical basis. The accommodation for near vision and for far vision with negative lenses is associated with the increased convexity of the lens of the eye as well as with the greater depth of focus which accompanies constriction of the pupil. The accommodation for far vision with positive lenses can be explained by the greater depth of focus which accompanies constriction of the pupil.

According to the Snellen measurement at the usual illumination, no change of acuity occurred at any dosage. But, as suggested above, some persons, after the 2-drop dose of 0.1% TEPP, noted that they required more intense illumination of the chart in order to achieve the same 20/20 acuity which they had before dosage, whereas, with the test conducted at unvaried illumination intensity, the Ortho-Rater showed a definite loss of acuity at the highest dosage level, averaging about 2 scoring units from 12 to 10 (Snellen equivalent of 20/17 to 20/20 for far vision), for both eyes and for each eye separately at both near and far vision. This slight loss of acuity was most evident during the period (one hour after dosage) when the patients were complaining most of the effects of ciliary spasm, conjunctivitis, rhinitis, and headache. It is quite possible that the chemical irritative effects as well as the diminished light intensity inherent in the miosis may have contributed to this slight loss of acuity.

Depth perception was not changed significantly at any dosage as measured objectively or by subjective complaints.

TABLE 2.—*Ocular Tension in Millimeters of Mercury as Determined by Schiotz Tonometer Before and After 0.1% TEPP*

Case No.	1 Hr. After Peanut Oil		2 Hr. After TEPP	
	Right	Left	Right	Left
2	19	19	13	13
3	26	17	20	17
4	17	20	16	15
6	26	20	17	15
7	13	13	12	12
9	16	17	13	14
Mean	19.3	17.7	16.5	14.5

Three hours after the administration of 2 drops of 0.1% TEPP, the average ocular tension of the six men dropped 2.8 and 3.4 mm. of mercury in the right and left eyes, respectively, as compared with normal levels established after instillation of peanut oil. The changes are summarized in Table 1 and given in more detail in Table 2. The tension of one man was a high normal after peanut oil and showed a paradoxical rise after only 1 drop of 0.1% TEPP. After the completely separate test with 2 drops of the same concentration, his tension was found to be back to his high normal level, and this same high normal level was still present one month after the last instillation of TEPP.

The averages of the tests for vertical and lateral phoria at near and far vision varied little. However, each of the subjects showed what appeared to be significant shifts in lateral phoria, but not all in the same direction.

Erythrocyte and plasma cholinesterase level, color vision, and perimetry remained normal throughout the entire experiment.

In order to be sure that the effects of the experimentally induced miosis were essentially the same as those of miosis acquired under conditions of actual application of TEPP dust, two pilot volunteers were reexamined during the season of occupational exposure. The rechecks were performed two to two and one-half hours after one pilot applied 2800 lb. of 1% TEPP (plus 1.5% other ethyl phosphates) dust and the other pilot applied 4900 lb. of the same formulation. One pilot showed no notable differences in the test results after the occupationally acquired miosis as compared with results after experimentally induced miosis. The second showed a greater ability to accommodate as measured by negative lenses at the usual Snellen test distance of 20 ft. His ability to read 20/20 was maintained up through − 7.00 D. compared with — 4.50 D. when his miosis was experimentally induced. However, as measured by the Prince Rule, accommodation was less than when miosis was induced. This second pilot also complained of loss of acuity in the right eye only ("has a shade over it" or "things look fuzzy"). The Snellen chart showed no detectable loss of acuity in this right eye, but the Ortho-Rater indicated a drop from his level with induced miosis of 10 to 4 scoring units (Snellen equivalent 20/20 to 20/50) for far vision. The left eye maintained the same acuity of vision after miosis was produced experimentally and occupationally. His acuity for near vision in the right eye dropped even farther after occupational exposure, from a normal of 10 scoring units to 1 unit (Jaeger equivalent: 1 to 10). The reason for this wide difference of results in the two methods of measurement is not yet apparent. It is believed that the repeated loss of acuity in the right eye of this particular pilot indicates a visual defect peculiar to his optical system.

By means of the several studies described thus far, physical explanations were found to account for all the predicted and recognized effects of TEPP in the eye. The one complaint by operating pilots remaining to be explained was their inability to judge distance with self-assurance. Dr. George H. Henton, Ophthalmologist, of Portland, Ore., who reviewed the results of the tests, suggested the possibility that radically unequal accommodation due to the production of miosis in one eye only might produce such effects. This hypothesis was consistent with clinical experience with patients who are placed on unilateral miotic therapy for the first time and also consistent with the infrequency of the inability to judge distance among pilots experi-

encing miosis after commercial applications. Moreover, several instances of unilateral miosis were discovered among pilots who were recently exposed as well as in old records of exposures.

As a test of this hypothesis, the first volunteer in whom bilateral miosis had been produced was retested with unilateral miosis following instillation of 2 drops of 0.1% TEPP. All ophthalmic results following unilateral induction were essentially the same for the single treated eye as they were for each eye following bilateral treatment. However, this volunteer did feel a little uncertain in going down or climbing stairways for about 12 hours after the instillation.

Six more nonpilot volunteers were given abbreviated testing after induction of unilateral miosis in the left eye. The objective findings were essentially the same (for the treated eye) as were those for the six pilots described earlier, but the volunteers with unilateral miosis had subjctive complaints for about 24 hours after the induction. Four of the subjects had no idea what minor disturbances of vision might occur. Because their subjective complaints are not easily subject to classification or quantitation, they are listed here.

CASE 1.—"Indefinable obscuring in the left field of vision and sensation that the two eyes were not on the same plane vertically."

CASE 2.—"The ground is coming up at me." "I feel one-sided." (The morning after induction, this volunteer hit his thumb three times in 20 minutes while attempting to nail fruit boxes. He has done this work for three months before and two months after this incident without such errors of distance judgment.)

CASE 3.—"The pegs are blurred" (on Howard-Dolman, but performance normal). "I feel like I'm stepping farther than I'm actually going. I'm giddy yet this morning." (This patient felt sweaty, especially on the back of his legs, about one and one-half hours after the first drop of TEPP. He was slightly nauseated and had tightness in his chest. He was nauseated by odor of ether while passing recovery rooms. This patient had been treated previously for neurocirculatory asthenia.)

CASE 4.—"It feels like it [the eye] is hanging out." "I feel like my left eye is wide open; it is bigger than my right eye and yet it feels like it does no good to look through the left eye." (This man missed the first step when reentering his home after the test.) "On the next afternoon I had the feeling that my left eye stared straight ahead, wide open and saw nothing. However, when I close my right eye, the image in the left looks O.K."

CASE 5.—"It feels cockeyed after the second drop." "I fumbled the sugar bowl, while removing it from a shelf at head height. I almost dropped it and I spilled sugar."

CASE 6.—"I have a vague feeling of not seeing too well." (This volunteer missed a step and almost fell.)

Thus, all seven of the volunteers in whom unilateral miosis was induced complained of subjective inability to perceive distance properly with self-assurance or experienced fumbling, stumbling, or other sensorimotor accidents or both.

Similar complaints frequently occur among ophthalmological patients in whom unilateral mioses is induced for therapeutic reasons. Dr. F. W. Jobe, of the Bausch and Lomb Optical Company, pointed out that these results are doubtless physiologically the same as the Pulfrich effect described by Duke-Elder [3] and in other textbooks. The Pulfrich effect causes the subject with unequal light intensities in the two eyes to perceive moving objects falsely; thus a pendulum appears to rotate in an ellipse instead of in one plane.

The induced or occupationally acquired miosis lasted from 12 to 24 hours, as indicated by the failure of the pupil to react to light and in accommo-